



Armed Forces College of Medicine AFCM



2- Gluconeogenesis

BY

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**Lecturer of Medical Biochemistry
And Molecular Biology**

INTENDED LEARNING OBJECTIVES (ILOs)



By the end of this lecture the student will be able to:

1. Discuss the different regulatory mechanisms of gluconeogenesis
2. Mention the causes of impaired gluconeogenesis
3. Relate the biochemical function of biotin and its deficiency manifestations

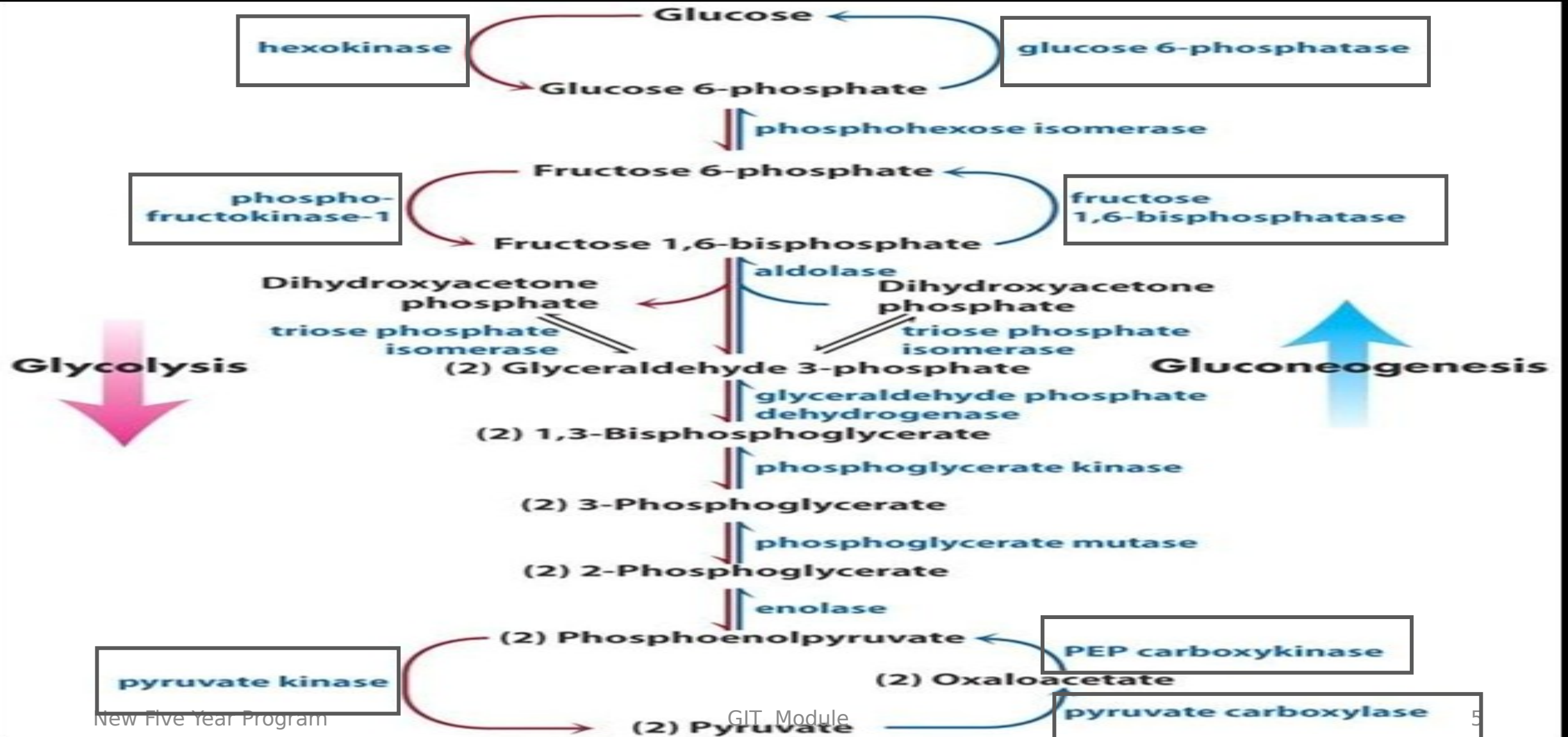
Outlines

Regulation of gluconeogenesis

Impaired gluconeogenesis

What is biotin?

Gluconeogenesis



Regulation of gluconeogenesis

Regulation of gluconeogenesis

**Gluconeogenesis & glycolysis are
Reciprocally Controlled**

In well fed state Glycolysis is active.

In Starvation the Gluconeogenesis is active.

Regulation of gluconeogenesis

The 4 regulatory enzymes of gluconeogenesis are:

1- Pyruvate carboxylase

2- PEPCK

3- Fructose 1,6 biphosphatase

4- Glucose 6 phosphatase

Regulation of gluconeogenesis

1-Long Term Regulation:

Gene regulation

2-Short Term Regulation

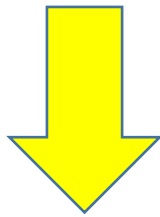
A- Allosteric

B- Substrate availability

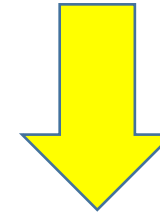
1-Long Term Regulation

During Fasting

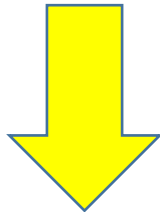
**Glucagon ,
epinephrine &
glucocorticoids**



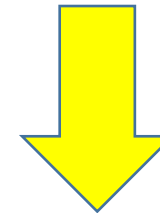
Induction



Repression



**4 key gluconeogenic
enzymes**

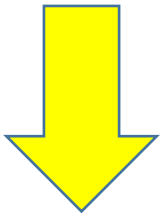


**3 key glycolytic
enzymes**

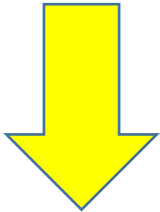
1-Long Term Regulation

During well fed

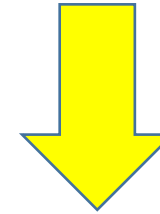
Insulin



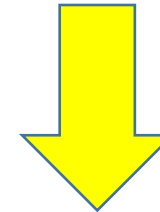
Induction



**3 key glycolytic
enzymes**



Repression



**4 key gluconeogenic
enzymes**

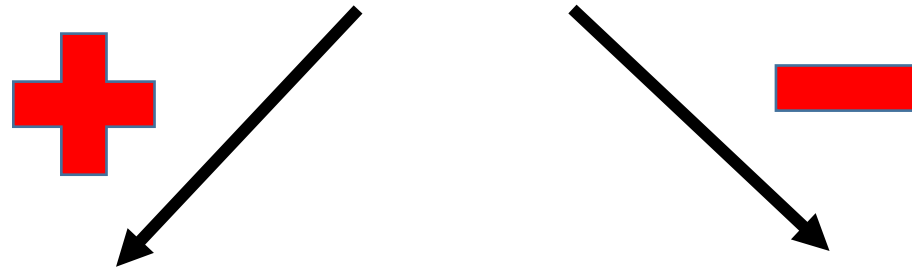
2-Short Term Regulation

A- Allosteric

regulation

1-Pyruvate Carboxylase

Acetyl CoA (↑ d.T fatty acid oxidation)



Pyruvate
Carboxylase

PDH

2-Short Term Regulation

A- Allosteric regulation

2-Fructose 1,6- biphosphatase

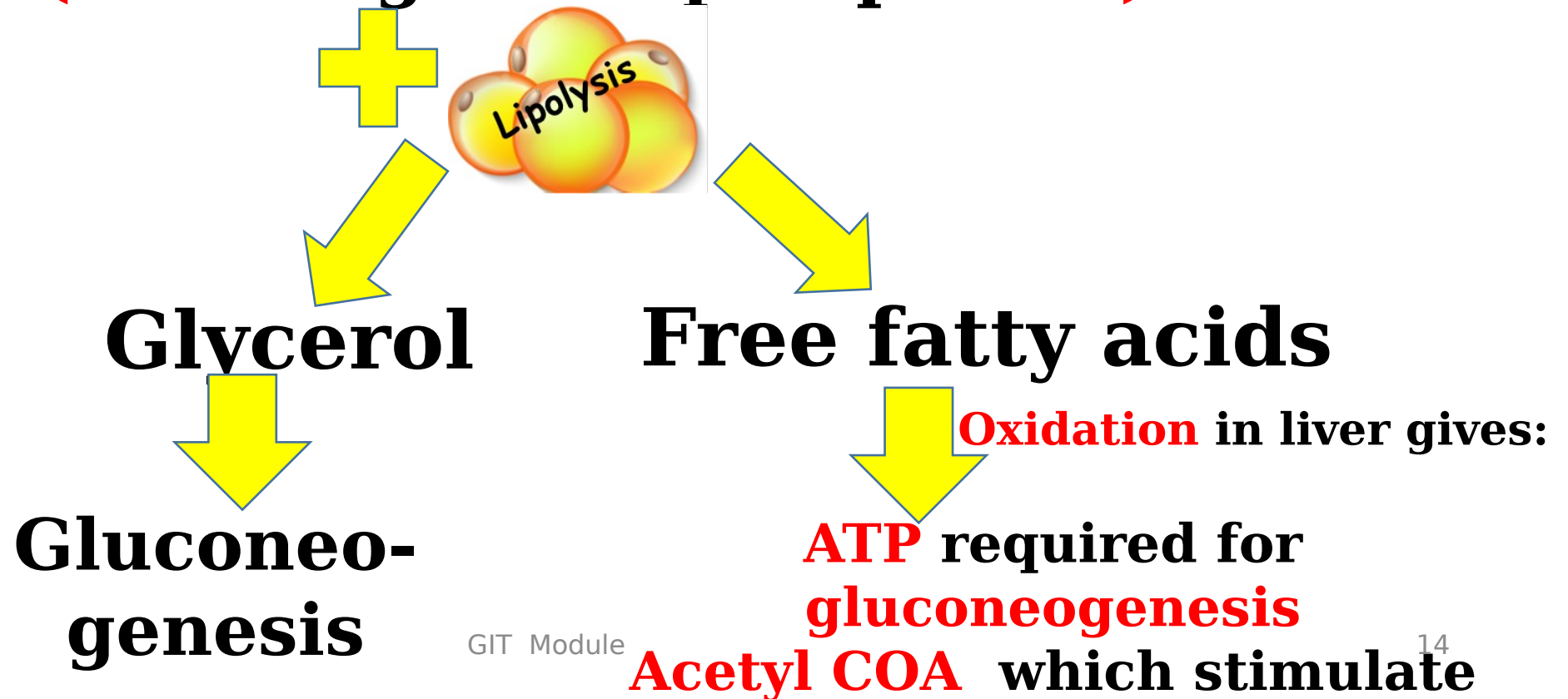
**Inhibited by AMP, inorganic
phosphate & fructose 2,6-
biphosphate**

2-Short Term Regulation

B- Substrate

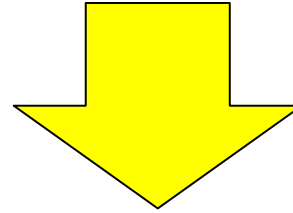
availability
During fasting

( **Glucagon & epinephrine**)



2-Short Term Regulation

B- Substrate
availability
Glucocorticoids



Promote **proteolysis** of muscle
proteins giving Glucogenic **amino**
acids

***N.B: Glucocorticoids induce genes for
transaminases enzymes***

Lecture Quiz



1-Which of the following is a positive allosteric modifier of the enzyme pyruvate carboxylase?

1. Biotin

2. Acetyl CoA

3. Oxaloacetate

4. ATP

5. GTP



2-Gluconeogenesis is inhibited by

- (A) Glucagon
- (B) Epinephrine
- (C) Glucocorticoids
- ☒ (D) Insulin



3- Pyruvate carboxylase is regulated by

- (A) Induction
- (B) Repression
- (C) Allosteric regulation
- (D) All of these**

Impaired gluconeogenesis

Impaired gluconeogenesis leads to

Fasting hypoglycemia & Lactic acidosis

Causes??

1- Inherited genetic defect in one of the following enzymes:

- Glucose 6 phosphatase (Von Gierk's)**
- Fructose 1,6 bisphosphatase**
- Carnitine deficiency primary and secondary**

2- Insufficiency of Glucocorticoids or glucagon

3- Liver cell damage

4- Chronic Alcohol consumption

Carnitine deficiency

Carnitine deficiency results in a **decreased ability of tissues to use LCFA as a source of energy.**

1ry carnitine deficiency:
=Congenital deficiency in any of *CPT OR CAT* system, during early childhood

***CPT-I* deficiency
(liver)**

***CPT-II* deficiency
(cardiac & skeletal ms)**



Primary carnitine deficiency

CPT-I deficiency (liver)

Inability to use LCFA as a source of energy this impairs Gluconogenesis leading to: **severe FASTING hypoketotic hypoglycemia, high level of blood carnitine, hepatomegaly, coma, & death**

CPT-II deficiency (cardiac & skeletal ms)

Cardiomyopathy & arrhythmia. Muscle pain (myalgia), Muscle weakness with myoglobinemia & myoglobinuria with red urine following prolonged exercise. damage the kidneys, in some cases leading to life-threatening kidney failure



Secondary carnitine deficiency

Causes:

- **Malnutrition patients (vegetarian)**
- **Liver disease Patients (decreased synthesis of carnitine)**
- **Hemodialysis patients (removes carnitine from the blood)**
- **Increased requirements for carnitine (pregnancy, severe infections, burns, or trauma)**

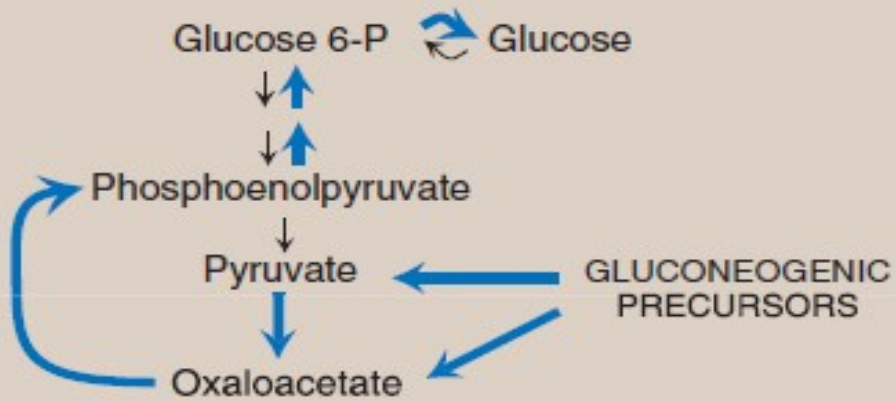
Clinical picture:

- **Muscle weakness, fatigue, hepatomegaly, fasting hypoglycemia, coma and death**

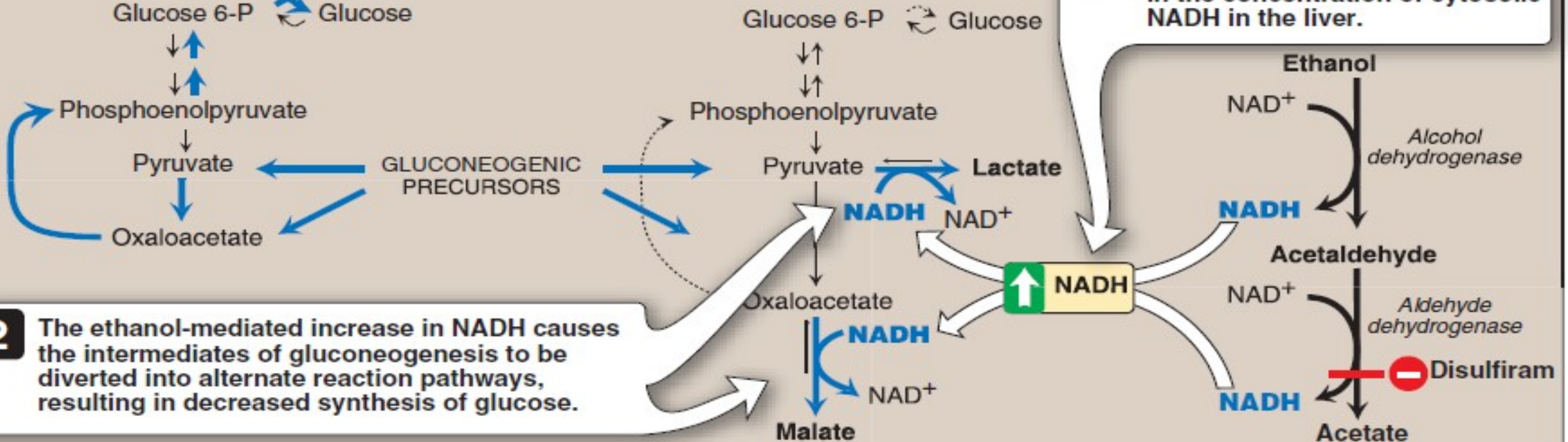


How Alcohol (ethanol) consumption impair gluconeogenesis process?

A No ethanol consumed



B Ethanol consumed



1 The metabolism of ethanol results in a massive increase in the concentration of cytosolic NADH in the liver.

2 The ethanol-mediated increase in NADH causes the intermediates of gluconeogenesis to be diverted into alternate reaction pathways, resulting in decreased synthesis of glucose.

The abundance of NADH favors the reduction of

- pyruvate to lactate &
- oxaloacetate (OAA) to malate



3-Ethanol decreases gluconeogenesis by

- (A) Inhibiting glucose-6-phosphatase**
- (B) Inhibiting PEP carboxykinase**
- (C) Converting NAD⁺ into NADH and decreasing the availability of pyruvate**
- (D) Converting NAD⁺ into NADH and decreasing the availability of lactate**

What is biotin?

Biotin

- **Biotin is an important component of enzymes involved in metabolizing fats and carbohydrates, influencing cell growth, and affecting amino acids involved in protein synthesis.**
 - **Biotin also called vitamin H**
- It acts as CO₂-carrier in CO₂ fixation reactions :**

I. Pyruvate carboxylase

II. Acetyl-CoA carboxylase

III. Propionyl-CoA carboxylase

Biotin

Biotin deficiency:

Biotin deficiency is rare.

Occurs due to:

- 1- Absence of the vitamin in the diet**
- 2- People that consume large amounts of raw egg. Egg white contains a heat labile protein (avidin) which can combine with biotin, preventing its absorption and producing biotin deficiency.**

Symptoms : anorexia, muscle pain, dermatitis, delayed growth, loss of hair , and depression

Explain the biochemical basis of Raw egg problem which occurs among people that consume large amounts of raw egg (athletes and body builders).

Case presentation

A 7-year-old girl, who lives on a farm, started to have shaking and sweating episodes. Upon physical examination, she was found to be hypoglycemic under fasting conditions (fasting blood glucose was 50 mg/dL) and positive for ketones in her blood and urine. Her growth curve is normal.

Case presentation

Further analyses showed no other metabolic abnormalities. Probing further into her history, in the absence of her parents, revealed that one of her chores was to collect eggs from the chicken coop every morning, and she had gotten into the habit of eating one or two raw eggs every morning. This had been going on for the past 6 weeks or so.

What is the reasonable explanation for her laboratory results?

Case Explanation

- Raw eggs contain a potent binding partner to biotin, **Avidin**
- Which, blocks biotin's participation in carboxylation reactions.
- This leads to reduced activity of **pyruvate carboxylase**, a necessary step in **many gluconeogenic pathways**

Case Explanation

- That leads to a reduced ability of the liver to properly maintain blood glucose levels.
- As **oxaloacetate** levels **drop** due to the need of oxaloacetate for gluconeogenesis,
- Acetyl-CoA derived from fatty acid oxidation increases, leading to ketone body formation.

When fatty acid β -oxidation predominates in the liver, mitochondrial pyruvate is most likely to be:

A. carboxylated to phosphoenolpyruvate for entry into gluconeogenesis

B. oxidatively decarboxylated to acetyl CoA for entry into ketogenesis

C. reduced to lactate for entry into gluconeogenesis

D. oxidatively decarboxylated to acetyl CoA for oxidation in Krebs cycle

E. carboxylated to oxaloacetate for entry into gluconeogenesis

Lecture Quiz



Which one of the following statements concerning gluconeogenesis is correct?

- A. It occurs in muscle.**
- B. It is stimulated by fructose 2,6-bisphosphate.**
- C. It is inhibited by elevated levels of acetyl CoA.**
- D. It is important in maintaining blood glucose during prolonged fasting.**
- E. It uses carbon skeletons provided by degradation of fatty acids.**

Take Home Message

- **Gluconeogenesis:**
Synthesis of glucose from noncarbohydrates
Anabolic & Energy-consuming
- **Four unique enzymes are required for the reversal of the 3 irreversible reactions of glycolysis**
- **Both gluconeogenesis & glycolysis are reciprocally-regulated**
- **Impaired gluconeogenesis leads to fasting hypoglycemia and may cause lactic acidosis**

SUGGESTED TEXTBOOKS



1. Lippincott's illustrated reviews in Biochemistry (6th edition) p. 228 & p.233-236 for Biotin and Regulation of Gluconeogenesis.

*Thank
you*



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